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EXAMINER	
SCHLAPKOHL, WALTER	
ART UNIT	**PAPER NUMBER**
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,100	ERLANDER ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	waf

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/4/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *12,13,19,28,37,38,44,46,47 and 70-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-11,14-18,20-23,25-27,29-33,35,36,39,40,42,43,54-56,58-63 and 65-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 December 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/31/05, 7/26/05 & 5/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 7-11,14-18,20-23,25-27,29-33,35,36,39,40,42,43,54-56,58-63 and 65-69.

DETAILED ACTION

Receipt is acknowledged of the papers filed 12/4/2006. Claims 7-23, 25-33, 35-40, 42-44, 46-47, 54-56, 58-63 and 65-73 are pending. Claims 12-13, 19, 28, 37-38, 44, 46-47 and 70-73 are withdrawn. Claims 7-11, 14-18, 20-23, 25-27, 29-33, 35-36, 39-40, 42-43, 54-56, 58-63 and 65-69 are under examination in the instant Office action.

Election/Restrictions

Claims 12-13, 19, 28, 37-38, 44, 46-47 and 70-73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/4/2006.

Applicant's election with traverse of Group I (claims 8-11, 15-18, 20-22, 25-27, 29-31, 54, 56, 58-62 and 68-69) in the reply filed on 12/4/2006 is acknowledged.

Applicant understands that the restriction requirement indicates that should Group I or Group II be elected, linking claims 7, 14 and 23 will be examined with the elected Group and should the linking claims be found allowable, the claims of the

remaining Group will be rejoined. Applicant further understands that should any one of Groups II through VI be elected, linking claims 32 and 39 will be examined with the elected Group and should the linking claims be found allowable, the claims of all remaining Groups will be rejoined. However, Applicant notes that there is no recognition in the restriction requirement that if Groups I and II are linked while Groups II through VI are linked, then Groups I and II through VI must also be linked. Therefore, Applicant believes that if Groups I and II are rejoined, then the corresponding linked claims of Groups III through VI must also be rejoined.

Applicant's traversal of the restriction requirement is on the ground(s) that the separation of the claims in Groups I and II appears to reflect a failure to recognize the presence of genus claims. Applicant further traverses the restriction requirement on the grounds that the Group I invention, drawn to a method comprising assaying a sample of breast cancer cells from a subject for the ratio of HoxB13 and IL17BR, does require the particulars of the Group III and V Inventions which are drawn to methods comprising assaying a sample of breast cells from a subject for increased or decreased expression of IL17BR polynucleotides (Group III) or HoxB13 polynucleotides (Group V) alone. Therefore, Applicant asserts, the restricted Inventions

separated but related as combination/subcombination do not meet both criteria required to demonstrate that the inventions are distinct, wherein the criteria are 1) the combination as claimed does not require the particulars of the subcombination as claimed, and 2) the subcombination has utility by itself. Finally, Applicant asserts that, contrary to the restriction requirement, the sequences featured in claim 54, 55, 58-62 and 65-67 are all either those of HoxB13 or IL13BR as encompassed by the genus claims. Accordingly, Applicant argues, the attempt by Examiner to assert that the sequences are 'different and distinct' is an improper attempt to avoid the standards reflected in *In re Weber* (580 F.2d 455) and *In re Haas* as well as the discussion at MPEP 803.02.

Applicant's arguments have been found persuasive in part for the following reasons. Applicant's arguments with regard to the presence/recognition of genus claims are found persuasive. Examiner acknowledges for the record that claims 7-9, 14-16, 20-23, 25, 29-33, 39-40, 56, 63 and 68-69 are genus claims.

Applicant's argument with regard to the combination/subcombination relationship between Inventions I and III & V and Inventions II and IV & VI has been found persuasive and Examiner has agreed to rejoin Groups III and V (claims 32-

33, 35-36, 39-40, 42-43, 55, 63, 65-67) with elected Group I for examination herein.

Applicant's understanding of the relationship among the linked inventions is correct insofar as Groups I and II are linked by claims 7, 14 and 23. Group II will be rejoined and examined with the elected Group should the linking claims be found allowable. However, Applicant's understanding that should any one of Groups II through VI be elected, linking claims 32 and 39 will be examined with the elected Group and should the linking claims be found allowable, the claims of all remaining Groups will be rejoined was incorrect based on the restriction requirement sent 11/2/2006. This is perhaps due to the presence of a typographical error on page 11 of the requirement for election/restriction mailed 11/2/2006 in which Examiner regretfully stated that "[c]laims 32 and 39 link inventions II-VI" when Examiner should have instead stated that claims 32 and 39 link inventions III-VI." However, it appears clear from the record that this statement erroneously and unintentionally included Group II as linked by claims 32 and 39 since none of the dependent claims listed in the Group II invention were dependent upon either of the stated linking claims 32 or 39. Furthermore, because there is no overlap among linked cases, there was no recognition in the restriction requirement that if

Groups I and II are linked and Groups II through VI are linked, then Groups I and II through VI must also be linked. The lack of such recognition is also an indication that the inclusion of Group II in the listing of those cases as linked by claims 32 and 39 was in error.

Nevertheless, this understanding is now rendered moot as Examiner has agreed to rejoin Groups III and V with elected Group I. The rejoinder, along with recognition of the listed genus claims, results in linkage of (now elected) Groups I, III and V with Groups II, IV and VI-VIII via linking claims 7-9, 14-16, 20-23, 25, 29-33, 39-40, 56, 63 and 68-69.

Finally, Applicant's election of SEQ ID NOS: 6 and 1 as representative HoxB13 and IL17RB sequences is acknowledged as is Applicant's assertion that "the sequences featured in claims 54, 55, 58-62, and 65-67 are all either those of HoxB13 or IL17RB as encompassed by the genus claims" (see page 11, last full paragraph of the Remarks filed 12/4/2006). Because the claimed SEQ IDS are dependent upon a genus claims, Examiner agrees to rejoin the recited sequences upon the allowance of the genus claims(s).

The requirement is still deemed proper and is therefore made FINAL.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/504,087, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Application No. 60/504,087 as originally filed does not provide support for the invention as now claimed: "[a] method to determine clinical outcome of a breast cancer afflicted subject, said method comprising assaying a sample of breast cancer cells from said

subject for the ratio of HoxB13 and IL17BR expression levels" (claim 7); or "[a] method of determining prognosis of a subject having ER+ breast cancer, or of a subject afflicted with ER+ breast cancer, said method comprising: assaying a breast cancer cell sample from said subject for the ratio of HoxB13 and IL17BR expression levels" (claim 14); or "[a] method to determine therapeutic treatment for an ER+ breast cancer patient based upon said patient's expected response to tamoxifen treatment, said method comprising determining an expected response to tamoxifen treatment for said patient by assaying a sample of breast cancer cells from said patient for the ratio of HoxB13 and IL17BR expression levels; and selecting the appropriate treatment for said patient" (claim 23). The 60/504,087 application does not provide sufficient blazemarks nor direction for the instant method steps encompassed by the above-mentioned limitation, as currently recited. The instant claims now recite a limitation, which was not clearly disclosed in the prior application as filed. Such a limitation recited in the present claims, which did not appear in the prior application, introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. 112.

Drawings

The drawings are objected to because Figures 1, 2, 5 and 7 are not drawn such that the curve for "responders" and "non-responders" can be distinguished. Moreover, Figures 3 and 6-7 comprise graphs which have unlabeled axes. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, Applicant will be notified and informed of any required corrective action in the next Office

action. The objection to the drawings will not be held in abeyance.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences are set forth in the specification that lack sequence identifiers (see Appendix listing of sequences presented as GenBank accession numbers). Applicant is required to comply with all of the requirements of 37 CFR 1.821 - 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F. R. 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Specification

The disclosure is objected to because of the following informalities: the disclosure comprises numerous tables which

are not labeled with a number (see, e.g., tables on 25-27, 36-38, etc.).

Appropriate correction is required.

Claim Objections

Claim 14 is objected to because of the following informalities: claim 14 recites "ER+ breast cancer" in line two; this abbreviation should be spelled out at its first occurrence in the claims.

Claim 22 recites "[t]he method of claim 14 wherein said sample is a section of tissue from a subject or are cells microdissected from said section" in lines 1-2 (emphasis added). Similarly, claim 31 recites "[t]he method of claim 23 wherein said sample is a section of tissue from a subject or are cells microdissected from said section" in lines 1-2 (emphasis added). Claims 22 and 31 are objected to because the claims lack proper subject/verb agreement.

Claim 26 is objected to because it comprises non-elected subject matter.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-11, 17-18, 23, 26-27, 32-33, 39-40, 43, 54-55, 58-62 & 65-67, and therefore dependent claims 25, 29-31, 35, 42 & 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites "[t]he method of claim 7 wherein said assaying for the expression levels of HoxB13 and IL17BR comprises detection of nucleic acids derived from a sample of breast cancer cells" in lines 1-3 (emphasis added). Claim 10 is vague and indefinite in that the metes and bounds of nucleic acids "derived from" a sample of breast cancer cells are unclear. What steps are involved in the deriving? Without some indication of the steps or methods involved in the deriving, it is not clear what structures/phenoyptes/characteristics are associated with or encompassed by the genus of nucleic acids "derived from" a sample of breast cancer cells.

Similarly, claims 11, 17-18 and 26-27 all recite nucleic acids "derived from" a sample. These claims are vague and indefinite as explained above.

Claim 23 recites "[a] method to determine therapeutic treatment for an ER+ breast cancer patient based upon said patient's expected response to tamoxifen treatment, said method comprising determining an expected response to tamoxifen treatement for said patient by assaying a sample of breast cancer cells from said patient for the ratio of HoxB13 and IL17BR expression levels; and selecting the appropriate treatment for said patient" in lines 1-7 (emphasis added). Claim 23 is vague and indefinite in that the metes and bounds of "the appropriate treatment" are unclear. Does Applicant intend treatment with adjuvant tamoxifen vs. no treatment at all, treatment of any kind, including a decision NOT to treat the patient; treatment of the patient with some an antiestrogen compound; or treatment comprising any anticancer therapy?

Claim 32 recites "[a] method to determine clinical outcome of a human subject having breast cancer, said method comprising assaying a sample of breast cells from said subject for increased or decreased expression of IL17BR or increased expression of HoxB13" in lines 1-4 (emphasis added). Claim 32 is vague and indefinite in that it is not clear what standard is

being used to determine whether IL17BR expression has been increased or decreased. Similarly, it is not clear how "increased" expression of HoxB13 is being determined. Does Applicant intend such a method wherein the expression is increased compared to a normal subject's breast cell, compared to the subjects own breast cells at a prior time point, or to some other standard?

Similarly, claim 39 recites a method comprising "assaying a sample of breast cells from said subject for increased expression of human HOXB13 sequences or increased or decreased expression of IL17BR" sequences. Claim 39 is vague and indefinite as explained for claim 32, above.

Regarding claims 33, 36, 40 and 43 the phrase "such as" renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 54 recites "[t]he method of claim 7, wherein said assaying for expression of an IL17RB sequence is of a sequence selected from SEQ ID NOS: 1, 2, 3, or 8" in lines 1-2 (emphasis added). Claim 54 is vague and indefinite in that it is not clear which sequences are actually being assayed or even how such sequences are being used in the assay. For example, does Applicant intend the method of claim 7, wherein said assay

comprises the detection of IL17RB sequences selected from the group consisting of SEQ ID NOs: 1, 2, 3, or 8; or does Applicant intend the method of claim 7, wherein SEQ ID NOs: 1, 2, 3 or 8 are used to determine IL17RB expression levels?

Similarly, claims 55, 58-62 and 65-67 recite methods comprising assaying for expression of either "an" IL17RB or "a" HoxB13 sequence "of a" sequence selected from a group of specific SEQ ID NOS. These claims are vague and indefinite as explained above.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-11, 14-18, 20-23, 25-27, 29-33, 35-36, 39-40, 42-43, 54-56, 58-63 and 65-69 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Sequences encompassed within "HoxB13" and "IL17BR" which are critical or essential to the practice of the invention are not enabled by the disclosure. See In re Mayhew, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The GenBank Accession numbers, UniGene cluster numbers and I.M.A.G.E. Consortium numbers taught in the

specification as HOXB13 and IL17BR sequences refer to entries in an electronic database which is subject to change over time. "Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication which patent or patent application publication does not itself incorporate such essential material by reference. In the instant case, the claims are, in effect, incorporating the sequences associated with GenBank Accession numbers, UniGene cluster numbers and I.M.A.G.E. Consortium numbers by reference to the entries in the electronic databases. While the specification teaches that at least the GenBank sequences have been included in the Appendix, it remains unclear which sequences of those that have been incorporated by reference are presently disclosed in the specification and/or are present in the sequence listing. Furthermore, "[w]hile the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such detail, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." See MPEP 608.01(p)[R-3]. Accordingly, insofar as Applicant's invention includes sequences which have only been disclosed by way of reference to the GenBank Accession numbers, Unigene

numbers and I.M.A.G.E. consortium numbers, Applicant has not provided the features that are critical or essential to the practice of the claimed invention.

If Applicant seeks to correct the sequences improperly incorporated by reference, Applicant must include a complete sequence listing as well as comply with the rest of the requirements of 37 CFR 1.821 through 1.825 (see above). However, this is NOT an invitation for Applicant to submit sequences that would be considered new matter. It is further noted that the nature of the noncompliance with the requirements of 37 C.F. R. 1.821 through 1.825 did not preclude examination on the merits in this case.

Claims 7-11, 14-18, 20-23, 25-27, 29-33, 35-36, 39-40, 42-43, 54-56, 58-63 and 65-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of

working examples, state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The instant claims are drawn to a method of determining the clinical outcome of a breast cancer afflicted subject wherein the method comprises assaying a sample of breast cells for the ratio of HOXB13 and IL17BR expression levels or for a change in the expression level of either gene alone (although where the ratio of HOXB13 and IL17BR ratio is used, Applicant has limited the claims to the use of breast cancer cells). Some claims are further limited to such methods wherein the RNA levels are measured with the use of an array or wherein the nucleic acids are prepared by mRNA amplification or quantitative PCR. Some claims are also further limited to such methods wherein the HOXB13 and/or IL17BR expression levels are used to determine the expected response to tamoxifen (TAM) treatment or to determine the prognosis of a subject having estrogen receptor positive (ER+) breast cancer or to determine the appropriate treatment for an ER+ breast cancer patient based upon the patient's expected response to tamoxifen treatment as determined by the HoxB13 and IL17BR expression levels. As

stated above, some claims are further limited to such a method wherein the cells are breast cancer cells. The invention is complex in that it involves measuring the expression levels of one or two genes in a breast cell sample such that their expression levels alone are indicative of a clinical outcome/prognosis/appropriate treatment course. The nature of the invention requires knowledge of a correlation between the expression of any sequence identified as a HOXB13 and/or an IL17BR sequence in any breast cell sample and the predisposition of a patient from which the sample was taken to a given clinical outcome. The nature of the invention requires that such a correlation can be made by using a sample comprising any given breast cell.

Breadth of the claims: The claims are extremely broad in that they encompass the diagnosis of any clinical outcome of any breast cancer afflicted subject. The assay comprises the measurement of any HoxB13 or IL17BR sequence from any sample of breast cells. The claims also encompass the measurement of HOXB13 and IL17BR levels at any time in the course of breast cancer and the determination of a prognosis and/or the selection of any "appropriate" treatment based upon the information obtained from any ratio of HOXB13 and IL17BR expression levels or any change in the level of HOXB13 and/or IL17BR exression

alone. In other words, the gene expression levels can differ by any amount. The large breadth of the claims exacerbates the complexity of the invention.

Guidance of the specification/The existence of working examples: The specification provides a number of HoxB13 and IL17BR sequences and teaches (by way of example) that any sequence, or unique portion thereof, of the … IL17RB sequence, identified by AF208111 or AF208111.1, may be used in the practice of the invention" and goes on to disclose the IL17RB sequence of SEQ ID NO: 3 (see pages 28, lines 1-3 and SEQ ID NO:3 on page 28-29). Similarly, the specification teaches, also by way of example, that "any sequence encoding all or part of the protein encoded by any IL17RB sequence disclosed herein may be used" (page 22, lines 15-18). In Example 1, the specification teaches that a 22,000-gene high-density oligonucleotide microarray was used to determine gene expression patterns from 62 ER+ breast cancer patients who were uniformly treated with tamoxifen (see page 55, lines 1-16). The IL17BR and HOXB13 oligonucleotide sequences used in the microarray are undisclosed. Thirty-three patients recurred while 29 patients remained disease free during a 14-year follow-up period (ibid). 149 genes were identified as correlative with tumor recurrence vs. non-recurrence, among them IL17BR and HOXB13 (see Table 1 on

pages 55-59). The specification further discloses that samples from 60 ER+ breast cancer patients treated with adjuvant tamoxifen were selected based on treatment outcome and teaches that "28 had developed tumor recurrence with a median time of 4 years, and 32 remained disease-free with a median follow-up of 10 years (Table 3)" (pages 65-66, especially page 65, lines 5-8). The specification concedes that "[p]atients who remained disease-free during the entire follow up period were likely to represent responders to TAM, although a small subset of them might have been cured by surgery alone" (page 65, lines 8-9). Statistical analysis on the gene expression differences among whole tissue sections from "responders" and "non-responders" yielded 19 genes with a p value at a cutoff of 0.001 (see page 7, lines 11-20 and Table 4 on pages 67-68). Again, HOXB13 and IL17BR were included among those identified (ibid). Gene expression patterns from laser capture microdissected (LCM) cells from the same patients were also tested (ibid). HOXB13, IL17BR, and CACNA1D expression was found to be significantly correlative in both the LCM and whole tissue section samples (see page 70, lines 5-14). The specification further concedes that "[t]he significant correlations of CACNA1D, HOXB13 and IL17BR with TAM treatment outcome suggest that these three genes may be novel predictors of TAM response" (page 70, lines 15-16;

emphasis added). Finally, in an effort to establish whether HOXB13, IL17BR13, and CACNA1D biomarkers could identify "ER+, TAM responders and non-responders", Applicant performed receiver operating characteristic (ROC) analysis and multivariate analysis (see pages 70-74). The results, according to Applicant, "demonstrate that the three genes identified in this study were strong independent predictors of treatment outcome by adjuvant therapy independent of known clinicopathological parameters" (see paragraph bridging pages 73-74).

The specification does not teach what levels of expression of HOXB13 and IL17BR sequences are required such that the ratio is indicative of any given clinical outcome, even response to adjuvant tamoxifen therapy.

The specification does not teach what increases in HOXB13 expression are required such that the increase is indicative of any given clinical outcome, even response to adjuvant tamoxifen therapy; nor does the specification teach how such an increase should be determined, i.e. whether the increase represents an increase within a patient's own sample over time or whether the standard upon which the "increase" is ascertained is based on some other standard. The same is true for the claimed "increase or decrease in expression of IL17BR.

The specification does not provide any statistical analysis of the expression level of HOXB13 and IL17BR sequences or even a ratio of such expression levels for patients who were NOT treated with tamoxifen.

The specification does not differentiate which HOXB13/IL17BR expression levels are indicative, or even teach how to use HOXB13 and IL17BR ratios, such that any prognosis of a subject with ER+ breast cancer can be determined and an appropriate treatment can be selected.

State of the prior art: The literature does report an example of a gene expression profile which is predictive of "a short interval of distant metastases" in breast cancer referred to as a "poor prognosis" signature (van't Veer et al, *Nature* **415**:530-536, 2002; IDS Ref BH; see entire document, especially the Abstract). This signature was derived from a test of 98 primary breast cancers from node-negative patients and consisted of 70 genes including those regulating cell cycle, invasion, metastasis and angiogenesis (ibid and page 530, 2nd column, 1st full paragraph). van't Veer et al also teach that, prior to their study, none of the signatures of breast cancer gene expression reported allowed for patient-tailored therapy strategies" (see page 530, 1st column, 1st paragraph). Moreover, Applicant concedes in the specification that while estrogen

receptor status is a powerful predictor of response to TAM (60% of ER+ tumors respond to TAM, whereas <10% of ER- tumors respond to the same treatment), "among ER+ tumors, no established predictors exist to identify the 40% non-responders" (page 70, lines 16-19). Thus, the state of the art is underdeveloped with respect to the use of a gene expression profiles generally (much less the use of only IL17BR and HOXB13 sequences) to predict breast cancer outcome.

Predictability of the art/Amount of experimentation necessary: The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art by Wu (*J. Pathol.* **195**(1):53-65, 2001.). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of "post genomics" informatics, including gene networks, gene pathways, and gene ontologies (page 53, left column). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63 - Discussion). Additionally, post-filing art reveals that most

gene association studies are typically wrong. Lucentini (The Scientist, page 20, Dec. 20, 2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (middle column, 1st full paragraph).

The lack of predictive success of gene expression studies may, in part, be due to the fact that increased mRNA is not always indicative of protein expression levels. Chen et al (*Molecular and Cellular Proteomics* **1**:304-313, 2002) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (page 304) and "it is not possible to predict overall protein expression

levels based on average mRNA abundance in lung cancer samples" (pages 311-312).

Most significantly, post-filing art does report the use of HOXB13 and IL17BR to attempt to predict clinical outcome in breast cancer patients treated with tamoxifen (Ma, et al. *Cancer Cell* **5**:607-616, 2004; IDS Ref BI). This study also discloses a study in which gene expression profiles of ER+ primary breast cancers treated with adjuvant tamoxifen therapy were generated (see entire document, especially the Abstract). However, Ma et al conclude that "[t]he observation that a simple expression ratio of two genes, HOXB13:IL17BR, accurately predicts tumor recurrence in adjuvant tamoxifen-treated patient with early-stage ER-positive breast cancer is limited by the size of patient cohorts" and that it "will require confirmation in a large population-based cohort" (paragraph bridging pages 612-613). Moreover, Ma et al concede that "it remains to be determined whether this two-gene ratio predicts a tumor's response to tamoxifen or its intrinsic aggressiveness, or both" and that a "similarly case-matched cohort of untreated patients will be required to address this issue" (ibid). This level of unpredictability is exacerbated by the fact that "little is known about the relevance of HOXB13 in breast cancer biology", and further that "[l]ittle information exists in the literature

linking IL17BR to breast cancer" as further taught by Ma, et al (page 611, 2nd column, 1st full paragraph and page 613, 1st column, 1st full paragraph).

Given the complex nature of invention and the underdeveloped state of the art at the time of filing, there would be a large and prohibitive amount of experimentation required to make and use the claimed invention. First, one would have to establish that HOXB13 and IL17BR sequences were predictive of clinical outcome in patients NOT treated with tamoxifen, both alone and in combination (as a ratio). Second, one of ordinary skill in the art would then have to determine which levels of HOXB13 and IL17BR expression were indicative of any given clinical outcome/diagnosis/treatment course selection. Such testing is not routine and would require a burdensome and undue amount of trial-and-error experimentation.

Claims 7-11, 14-18, 20-23, 25-27, 29-33, 35-36, 39-40, 42-43, 54-56, 58-63 and 65-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

NOTE: For purposes of this rejection only, claims 54-56, 58-62 and 65-67 have been interpreted to include fragments of the recited sequences (see discussion below).

The claims are drawn to HoxB13 and IL17BR sequences. Some claims are further limited to sequences comprising at least 24 nucleotides from the 3′ untranslated region, the coding region, or the 5′ untranslated region, of human HOXB13 or IL17BR. With regard to sequences encompassed by IL17BR, the specification teaches that "any sequence, or unique portion thereof, of the IL17RB sequences of the [I.M.A.G.E. Consortium NM 018725 and NM 172234] cluster, as well as the UniGene *Homo sapiens* cluster Hs.5470, may be used. Similarly, any sequence encoding all or part of the protein encoded by any IL17RB sequence disclosed herein may be used" (page 22, lines 15-18). On pages 25-27, Applicant lists I.M.A.G.E. Consortium Clone ID numbers and the corresponding GenBank accession numbers of IL17BR sequences identified as belonging to the I.M.A.G.E. Consortium and UniGene clusters. The specification further teaches that "sequences that are not identified as having a Clone ID number but still identitied as being those of IL17RB" are also included and that "[t]he sequences include those of the 'sense' and complementary

strand sequences corresponding to IL17RB" (page 25, lines 1-2). The sequence of each GenBank accession number is presented in the Appendix. The specification also provides two consensus sequences for IL17RB (see page 22-24, SEQ ID NOS: 1 and 2). Finally, the specification teaches that in a preferred embodiment, "any sequence, or unique portion thereof, of the following IL17RB sequence, identified by BC007092, may be used in the practice of the invention" and goes on to disclose the IL17RB sequence of SEQ ID NO: 3 (see pages 28, lines 1-3 and SEQ ID NO:3 on page 28-29). Similarly, with regard to sequences encompassed by HoxB13, the specification teaches that "any sequence, or unique portion thereof, of the HOXB13 sequences of the I.M.A.G.E. Consortium cluster NM_006361, as well as the UniGene Homo sapiens cluster Hs.66731, may be used. Similarly, any sequence encoding all or a part of the protein encoded by any HOXB13 sequence disclosed herein may be used" (page 35, lines 21-24). The specification further provides a consensus sequence for HoxB13 (see page 35-36, SEQ ID NO: 6). On pages 36-38, Applicant lists I.M.A.G.E. Consortium Clone ID numbers and the corresponding GenBank accession numbers of HoxB13 sequences identified as belonging to the I.M.A.G.E. Consortium and UniGene clusters. The specification further teaches that "sequences that are not identified as having a Clone ID number

but still identitied as being those of HOXB13" are also included and that "[t]he sequences include those of the 'sense' and complementary strand sequences corresponding to HOXB13" (page 36, lines 25-30). Finally, the specification teaches that in a preferred embodiment, "any sequence, or unique portion thereof, of the following HOXB13 sequence, identified by BC007092 or BC00792.1, may be used in the practice of the invention" and goes on to disclose the HOXB13 sequence of SEQ ID NO:7 (see pages 39, lines 1-29).

Thus, the claims encompass any sequence "identitied as being those of HOXB13" or "identitied as being those of IL17RB", which includes any sequence of the I.M.A.G.E. consortium cluster sequences or SEQ ID NOS which have been provided, such that the sequences can be used to assay a sample of breast cells to determine the level of HoxB13 and IL17BR expression. The claims also encompass any such sequences which are "derived from a sample of breast cancer cells" (see, e.g., claims 10-11). The claims do not provide any structural information with regard to the HoxB13 and IL17BR sequences capable of use in a method of determining clinical outcome of a breast cancer afflicted subject, such that the expression levels of HoxB13 and/or IL17BR can be assayed in such a way as to indicate any given clinical

outcome. Thus, the rejected claims comprise a set of nucleic acid sequences that are defined by their function.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. As already mentioned above, the specification provides a number of HoxB13 and IL17BR sequences and teaches by way of example, that any sequence, or unique portion thereof, of the … IL17RB sequence, identified by AF208111 or AF208111.1, may be used in the practice of the invention" and goes on to disclose the IL17RB sequence of SEQ ID NO: 3 (see pages 28, lines 1-3 and SEQ ID NO:3 on page 28-29). Similarly, the specification teaches, also by way of example, that "any sequence encoding all or part of the protein encoded by any IL17RB sequence disclosed herein may be used" (page 22, lines 15-18). In Example 1, the specification teaches that a 22,000-gene high-density oligonucleotide microarray was used to determine gene expression patterns from 62 ER+ breast cancer patients (see page 55, lines 1-16). No description is provided of the IL17RB or HoxB13 sequences used to identify IL17RB or

HoxB13 expression. The expression products measured for the determinative HoxB13/IL17BR ratio were identified as Accession Number AF208111 for IL17BR and Accession Number BC007092 for HOXB13 (see Table 1, pages 55-59). No unique portions of IL17RB or HoxB13 or fragments of IL17RB or HoxB13 that have been used in such a method were disclosed.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the results are not necessarily predictive of other sequences capable of use in such a method when considered in light of the large genus of sequences taught in the specification as encompassed withint those identified as HoxB13 and IL17BR sequences. Thus, it is impossible to extrapolate from the example(s) described herein those nucleic acid molecules that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of IL17BR or HoxB13 sequences capable of use in a method of determining clinical outcome breast cancer patient. In fact, in an article published post-filing, Ma et al teach that "[l]ittle is known about the relevance of HOXB13 in breast cancer biology"

(Cancer Cell, 5:607-616, 2004; IDS Ref BI; see entire document, especially page 613, 1st column, first full paragraph).

Given the very large genus of nucleic acid molecules encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the IL17BR and HoxB13 sequences capable of fulfilling the claim limitations of claims 7-11, 14-18, 20-23, 25-27, 29-33, 35-36, 39-40, 42-43, 54-56, 58-63 and 65-69, the skilled artisan would not have been able to describe the broadly claimed genus of IL17BR and HOXB13 nucleic acid sequences that either 1) can be used to determine gene expression levels of IL17BR or HOXB13 or 2) once expressed, can be measured such that the ratio is indicative of any clinical outcome of any breast cancer patient. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those nucleic acid sequences that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 7-11, 14-18, 20-23, 25-27, 29-33, 35-36, 39-40, 42-43, 54-56, 58-63 and 65-69.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7-8, 14-15, 32 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/089,097. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims encompass the measurement of HOXB13 and IL17BR expression levels in a cell sample. Claim 1 of the 11/089,097 application is drawn to the measurement of HOXB13, IL17BR, CHDH and/or QPRT

expression levels whereas claims 7-8 and 14-15 are drawn only to the measurement of HOXB13 and IL17BR, but claim 1 of 11/089,097 enompass the use of only HOXB13 and IL17BR as found in claims 7-8 and 14-15 of the instant application. Moreover, both sets of claims are drawn to the HOXB13 and IL17BR expression measurements in patient samples.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 7-11, 14-18, 20-23, 25-27, 29-31, 54, 56, 58-62 and 68-69 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-11, 14-19, 22-28, 31-35, 49-50, 52-63 of copending Application No. 11/089,097. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims encompass the measurement of HOXB13 and IL17BR expression levels in ER+ breast cancer samples such that either a clinical outcome or a prognosis can be determined, or a therapeutic treatment can be selected. Both sets of claims are drawn to such methods wherein the clinical outcome is determined if the patient is treated with an estrogen receptor modulator/antiestrogen compound/tamoxifen. Both sets of claims

are drawn to such methods wherein the nucleic acds are prepared either by mRNA amplification or quantitative PCR. Moreover, both sets of claims are drawn to such measurements wherein the samples were procured by either fine needle aspiration or microdissection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant is advised that should claim 21 be found allowable, claim 69 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

No claim is allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the

Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

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Patent Examiner
Art Unit 1636

February 2, 2007

DAVID GUZO
PRIMARY EXAMINER